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THEORETICAL REVIEW

Postoperative sleep disruptions: A potential catalyst of acute pain?

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SUMMARY

Despite the substantial advances in the understanding of pain mechanisms and management, postoperative pain relief remains an important health care issue. Surgical patients also frequently report postoperative sleep complaints. Major sleep alterations in the postoperative period include sleep fragmentation, reduced total sleep time, and loss of time spent in slow wave and rapid eye movement sleep. Clinical and experimental studies show that sleep disturbances may exacerbate pain, whereas pain and opioid treatments disturb sleep. Surgical stress appears to be a major contributor to both sleep disruptions and altered pain perception. However, pain and the use of opioid analgesics could worsen sleep alterations, whereas sleep disruptions may contribute to intensify pain. Nevertheless, little is known about the relationship between postoperative sleep and pain. Although the sleep–pain interaction has been addressed from both ends, this review focuses on the impact of sleep disruptions on pain perception. A better understanding of the effect of postoperative sleep disruptions on pain perception would help in selecting patients at risk for more severe pain and may facilitate the development of more effective and safer pain management programs.

Introduction

Despite significant advances in the understanding of pain mechanisms and innovative developments of analgesic and anesthetic agents, acute postoperative pain control remains a challenge in about one-third of surgical patients [1]. In a large Dutch cohort of 1490 surgical patients who received postoperative pain treatment, patients still experienced moderate to severe pain on the day of the surgery, which continued in 15% at four days after surgery [2,3]. Acute postoperative pain was also followed by chronic pain, which was severe in about 2–10% of postoperative patients [4]. In an attempt to improve postsurgical pain management, studies have identified several potential predictors of postoperative pain as well as several preoperative and psychological factors such as pain experience, age, duration, surgery, and previous chronic sleep problems (Fig. 1) [3,5–8]. Mamie et al. [7] found that, of several factors known to affect postoperative pain, chronic sleep complaints before surgery constituted the strongest determinant of pain at rest postoperatively. Moreover, patients frequently report postoperative sleep disturbances in response to surgical stress, and some electroencephalographic studies have demonstrated decreased total sleep time in both slow wave sleep (SWS) and rapid eye movement (REM) sleep duration as well as increased sleep arousals [9]. Furthermore, clinical observations largely indicate that sleep and pain interact bidirectionally. Thus, clinical and experimental studies have demonstrated that sleep disturbances exacerbated pain perception in healthy subjects [9–24] and in several pain conditions [25,26], whereas pain [27–30] and pain management with opioids [31,32] may disturb sleep. Surgical stress appears to be a major contributor to both sleep disruptions and altered pain perception, whereas sleep disturbances may alter pain perception and intensify pain postoperatively, and pain and the use of opioid analgesics may increase alterations in the quality and quantity of sleep. Although this bidirectional relationship between postsurgical sleep and pain has been addressed in this review, we focus on updating the state of the knowledge on the potential role of sleep disturbances in postsurgical pain exacerbation in the aim of helping in selecting patients at risk for more severe pain and facilitating the development of more effective and safer pain management programs.

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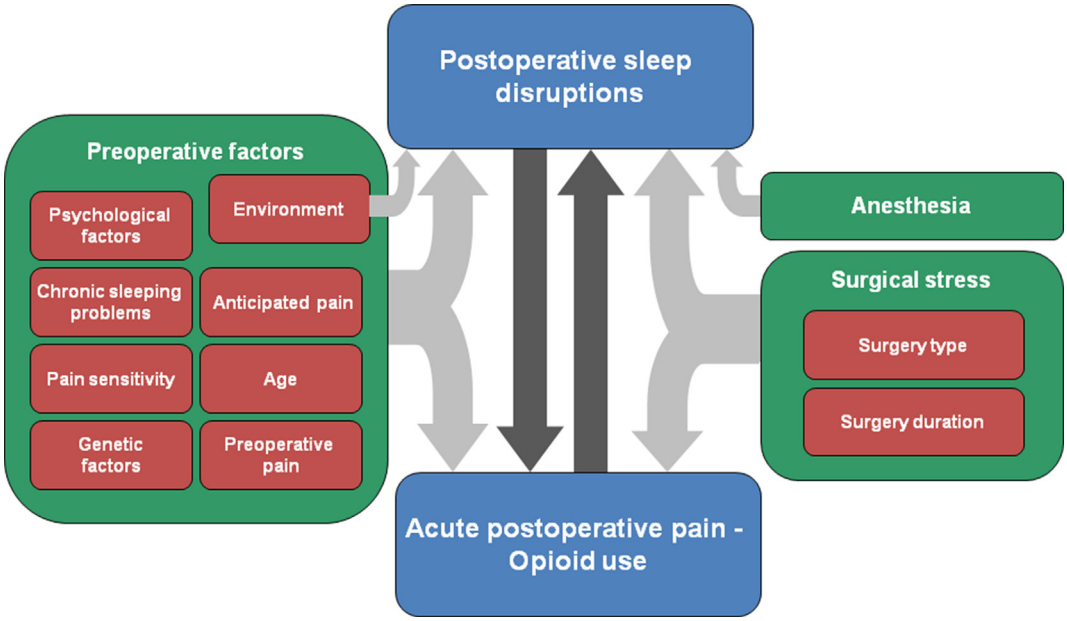

Fig. 1. Schematic diagram of the relationship between sleep disruptions, opioid use, and postoperative pain, and respective contributing factors. Filled arrows represent the relationship and clear arrows represent contributing factors.

This review is based on a documentary search of Medline and the Cochrane Library up to May 2013. Keywords used to research *sleep disruptions after surgery* were "sleep" associated with "surgery" or "postoperative." All studies conducted in humans were selected. Keywords used to research *the sleep–pain interaction* were "sleep," "sleep deprivation,", "sleep fragmentation," or "sleep disruption" associated with "pain" or "analgesia." Studies in both animals and humans were considered. Keywords for *sleep disruptions and pain in the postoperative period* were "sleep," "sleep deprivation," "sleep fragmentation," or "sleep disruption" associated with "pain" or "analgesia" and "surgery" or "postoperative." Additional inclusion criteria were appropriate statistical and methodological descriptions (e.g., sample size, sleep deprivation protocol, pain measurement).

Sleep disruptions after anesthesia and surgery

Postoperative sleep disturbances are frequently reported: 42% of patients complained of unsatisfactory sleep after orthopedic, vascular, and general surgery (vs. 28% the night before surgery), and their sleep remained unsatisfactory after four days in 23% of cases [33,34]. Notably, these patients reported the shortest total sleep time compared to before surgery. Fifteen days after surgery, one-quarter of patients again reported abnormal sleep, and 24% underwent hypnotic treatment [33]. Data from electroencephalographic studies have elucidated the nature of postsurgical sleep alterations (for details, see Table 1). In the first postoperative nights, sleep patterns can be severely disturbed, with marked decrease in total sleep time (six of 11 studies), decreased SWS duration (11 of 13 studies), and decreased REM sleep (12 of 13 studies), which are associated with frequent sleep arousals [4,9,22,23,35–44]. Disruptions in REM sleep and SWS were reported at up to total suppression of both SWS and REM sleep in several cases [9,22,23,35,36,38,39,41–43,45]. Overall, at least 41% and 19% of patients presented total SWS and REM sleep suppression, respectively, during at least one night after surgery (13 studies, Table 1). Altered sleep prevents normal sleep patterns and the associated sleep cycle rhythms: patients frequently reported that they napped during the day [33], and several exhibited REM sleep during their naps [39].

Sleep disruptions can persist up to three or four nights postsurgery [9,23,36,41,42,45], and longer: up to several weeks for cardiac surgery [44]. Thereafter, total sleep time and SWS duration gradually normalized to preoperative levels, and after several nights, and REM sleep rebound occurred [4,9,22,23,35–44]. Thus, profound disruptions, marked by sleep fragmentation, shorter total sleep time, and SWS and REM sleep deprivation occur postsurgery, with REM sleep rebound after several nights.

Putative factors in sleep disruption

Several factors may contribute to disturbed sleep patterns and sleep complaints after surgery (summarized in Fig. 1), including the environment, surgical stress, anesthesia, psychological factors, and pain [9]. The environment is often proposed as a disruptive factor [33,46]: hospital-related environmental factors, especially in *intensive care units* (ICUs), such as noise, light, postoperative inconveniences, and the activities of the health care staff, can contribute to disturbed postoperative sleep. Sleep fragmentation and decreased SWS and REM sleep were reported in an ICU [35], but were less marked than in the postoperative period, and this single factor could not explain all postsurgical sleep changes. Regarding surgical stress, the magnitude and duration of surgery have been related to sleep disturbances [9,38,44]. Although surgery duration was related to the duration of sleep complaints, especially in heart surgery [44], surgical trauma appears to be a major sleep disturbance factor, with potential mechanisms being endocrine, autonomic, and inflammatory stress responses to surgery [9,38]. The main known cytokines released after surgery are interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α), and IL-6 [47], known to disturb sleep with increased slow wave sleep duration and decreased REM sleep duration [48]. Sympathetic overactivity and high stress hormone release (e.g., cortisol and adrenocorticotropic hormones) could also disrupt sleep [49]. Anesthesia has also been shown to produce similar sleep disturbance patterns after surgery, including sleep fragmentation, shorter total sleep time, and SWS and REM sleep deprivation, irrespective of anesthetic technique (general vs. regional anesthesia) [43,45]. However, in healthy volunteers, general anesthesia (isoflurane during the day) had only a

Table 1
Polysomnographic studies postsurgery.

Authors	Type of surgery	Type of anesthesia	n	F/M	Preoperative nights	Postoperative nights	Total sleep time	REM sleep duration	REM sleep abolished[a]	SWS duration	SWS abolished[a]
Johns et al. 1974 [40]	Heart surgery or major abdominal surgery	General anesthesia	6	1/5	2–3	2–3	Decrease	Decrease	4	Decrease	0
Ellis and Dudley 1976 [38]	Abdominal surgery	General anesthesia	12	0/12	−1	1 and 2	Decrease	Decrease	4	Decrease	–
Orr and Stahl 1977 [44]	Open heart surgery and pneumonectomy	General anesthesia	9	0/9	−2 to −1	1–14	Decrease	Decrease	9	Decrease	9
Kavey and Altshuler 1979 [45]	Herniorrhaphy	General or local anesthesia	10	0/10	−1 and control group	1–3	Decrease	Decrease	5	Decrease	9
Aurell and Elmqvist 1985 [35]	Major non-cardiac surgery	General anesthesia	9	5/4	Control group ($n = 46$)	1–4	Decrease	Decrease	At least 1	Decrease	At least 1
Lehmkuhl et al. 1987 [43]	Minor surgery	General anesthesia	46	42/4	Control group ($n = 12$)	1	No change	Decrease	18	Decrease	0
Knill et al. 1990 [41]	Cholecystectomy Gastroplasty	General anesthesia	12	5/7	−2 to −1	1–6	No change	Decrease then increase	12	Decrease	0
Rosenberg et al. 1994 [22]	Major abdominal surgery	General anesthesia	10	4/6	−2 to −1	1–3	No change	Decrease then increase	At least 1	Decrease	10
Rosenberg-Adamsen et al. 1996 [23]	Laparoscopic cholecystectomy	General anesthesia	10	8/2	−1	1	No change	No change	1	Decrease	4
Edéll-Gustafsson et al. 1999 [37]	Coronary artery bypass grafting	General anesthesia	38	0/38	−2 to −1	1–2	Decrease	Decrease	At least 1	Decrease	0
Cronin et al. 2001 [36]	Gynecological surgery	General or local anesthesia	10	10/0	−1	3	–	Abolished then increase	10	Decrease	0
Gögenur et al. 2008 [39]	Major abdominal surgery	General anesthesia	11	2/9	−1	2	–	Decrease	9	No change	0
Krenk et al. 2012 [42]	Major orthopedic surgery	Spinal anesthesia	10	6/4	−1	1 and 2	No change	Decrease	2	No change	0

[a] Number of patients presenting full abolished sleep stage (SWS or REM sleep) for at least one night.

moderate effect on SWS and no effect on REM sleep [50]. Thus, in the absence of surgical stress, hospitalization, and postsurgical pain, anesthesia alone does not appear to trigger postsurgical sleep disturbances. Patients also frequently reported pain as a major sleep disturbing factor after surgery [33,46], and pain [46,51] as well as opioid use [31,36] have been reported to disturb sleep. Sleep disruptions present wide interindividual differences [52], possibly due to several confounding factors such as age, surgery duration, surgery type [9], and individual psychological and genetically preoperative vulnerability [53]. Preoperative anxiety, catastrophizing, and chronic sleep disorders could render patients vulnerable to hospitalization and surgery as well as pain [4,7]. These factors could contribute to the wide interindividual differences in the intensity and duration of reported sleep disturbances and complaints.

The sleep–pain interaction

The relationship between pain and sleep involves multiple unidirectional or bidirectional interactions in which acute and chronic pain are associated with sleep disruptions and disturbed or shortened sleep can in turn alter pain perception [25,26,54–58]. It is important to clarify that the bidirectional model of the impact of pain on sleep and of sleep on pain is not absolute. Some subjects could be more vulnerable to these effects, and in some situations, sleep quality is a better predictor of next-day pain, whereas in other situations, daytime hypervigilance is a better predictor [59].

Chronic painful conditions are frequently associated with sleep disturbances, including changes in sleep continuity and sleep architecture as well as increased daytime sleepiness [60]. In turn, sleep quality in chronic pain conditions was considered a consistent predictor of pain the next day [26]. This vicious cycle has also been reported by patients with chronic pain due to conditions such as fibromyalgia [58] or severe skin burns [25], although not for all chronic pain conditions [54].

In the general population, recent epidemiologic data also show a relationship between sleep duration and the frequency of next-day pain: transitioning from a night of relatively normal sleep duration (6–9 h) to a night of either fewer than 6 h or more than 9 h of sleep was related to substantial increases in next-day pain frequency [61]. Moreover, when subjects slept without sleep interruption, stage deprivation, or stage restriction (see following section for more details, and Tables 2 and 3), longer REM sleep duration was correlated with higher pain ratings on suprathreshold pain tests [62]. Recently, pain perception and daily reported pain were assessed in patients with primary insomnia [63]. Under heat and mechanical pain, insomnia patients presented decreased pain threshold compared to healthy volunteers. They also experienced more frequent and more intense pain and presented a dysfunctional pain-inhibition system, measured by a diffuse noxious inhibitory controls (DNIC) paradigm, in which perception of a main experimental pain is inhibited with parallel pain stimulation by endogenous pain pathway activation. Similarly, Roehrs and collaborators [21] found that lengthening sleep duration in healthy subjects increased the heat pain threshold (decreased pain sensitivity).

With respect to the pain–sleep interaction (sleep deprivation and its effect on the pain process or pain stimulation during sleep), the first experimental study of sleep deprivation and the consequences on pain perception was conducted in 1935 by Cooperman and collaborators [64]: in the absence of statistical analysis, they observed that total sleep deprivation (SD) induced a lower pain threshold in six healthy volunteers. Since this pioneering work,

Table 2
Studies on the effects of sleep deprivation on pain in healthy volunteers.

Authors	*n*	F/M	Design	Pain measurement	Methods	Recorded nights	Sleep intervention	Nights	Methods	Main results
Moldofsky et al. 1975 [19]	6	0/6	Repeated measurements	Mechanical stimulation	Algometer	7	Partial SWSD	3	Auditory stimulation	Increased reported pain response to stimulation
			B–SD–R	Daily reported pain-related discomfort	Questionnaire					Increased reported pain-related discomfort
							Recovery	2		Decreased reported pain response to stimulation Decreased reported pain-related discomfort
Moldofsky and Scarisbrick 1976 [18]	13	1/12	Repeated measurements	Mechanical stimulation	Algometer	7	Partial SWSD	3	Auditory stimulation	Increased reported pain response to mechanical stimulation
			B–SD–R	Daily reported pain-related discomfort	Questionnaire					Increased reported pain-related discomfort
			Two groups: REM SD and SWSD				REM SD	3	Auditory stimulation	No change
							Recovery	2		Decreased pain report to mechanical stimulation (SWSD)
Drewes et al. 1997 [65]	10	0/10	Repeated measurements B–SD	Mechanical and heat pain threshold	Thermode Pneumatic stimulator	1	Total SD	1	Kept awake	No change
Older et al. 1998 [69]	19	3/16	Repeated measurements	Mechanical pain threshold	Algometer	5	Partial SWSD	3	Auditory or physical stimulation	Decreased mechanical pain threshold (compared to controls but not to basal)
			B–SD–R	Daily reported pain-related discomfort	Questionnaire					Increased reported pain-related discomfort compared to controls (after third night)
			Two groups (control)				Recovery	1		No change
Lentz et al. 1999 [17]	12	12/0	Repeated measurements	Mechanical pain threshold	Algometer	4	Partial SWSD	3	Auditory or physical stimulation	Decreased mechanical pain threshold (after second night)
			B–SD	Daily reported pain-related discomfort	Questionnaire					Increased reported pain-related discomfort (after second night)
Arima et al. 2001 [12]	10	0/10	Repeated measurements	Mechanical pain threshold	Maximum voluntary occlusal force, Algometer	6	Partial SWSD	3	Auditory stimulation	No change
			B–SD–R	Daily reported pain-related discomfort	Questionnaire					
Onen et al. 2001 [20]	9	0/9	Repeated measurements	Mechanical and heat pain threshold	Thermode	6	Total SD	1	Kept awake	Decreased mechanical pain threshold but not for heat pain
			B–SD–R		Algometer		SWSD	2	Auditory or physical stimulation	No change
			Two groups: Total SD, then REM SD or SWSD (two weeks after)				REM SD	2	Auditory or physical stimulation	No change
							Recovery	1		Increased mechanical pain in total SD and SWSD but not for REM SD
Kundermann et al. 2004 [10]	20	9/11	Control group	Heat and cold pain threshold	Thermode	2	Total SD Two nights with one-night interval	2	Kept awake	Decreased heat pain threshold but not for cold pain
Haack and Mullington 2005 [14]	40	16/26	Repeated measurements B–SD–R with control group	Daily reported pain-related discomfort	Questionnaire	12	Partial SD	10	Sleep restriction Control with actigraphy	Increased reported pain-related discomfort (after second night to 12th night)

Roehrs et al. 2006 [11]	13	10/3	Two groups, several conditions	Finger withdrawal latency pain testing	Bulb	3–4	Total SD	1	Kept awake	Decreased finger withdrawal latency compared to Partial SD and control night
							Partial SD	1	Sleep restriction	Decreased finger withdrawal latency compared to control night
							REM SD	1	Woken during REM sleep	Decreased finger withdrawal latency compared to No REM SD and control night
							No REM SD	1	Woken during no REM sleep	No change
Haack et al. 2007 [63]	18	6/12	Control group	Daily reported pain-related discomfort	Questionnaire	15	Partial SD	12	Sleep restriction	Increased reported pain-related discomfort
Smith et al. 2007 [62]	32	32/0	Repeated measurements	Mechanical and cold pain perception threshold	Algometer	7	Forced awake	3	Woken during sleep	Increased reported pain-related discomfort
			B–SD–R	Diffuse noxious inhibitory controls	Water immersion					Decreased pain-inhibition function (after first night)
			Three groups: partial SD, forced awakening (then total SD), and control group	Daily reported pain-related discomfort	Questionnaire					No change in mechanical pain threshold (after 2nd night)
							Partial SD	3	Sleep restriction	No change
							Total SD	1	Kept awake	Increased reported pain-related discomfort No change in mechanical pain threshold No change in pain-inhibition function
							Recovery	1		Increased pain-inhibition function (forced awake) Decreased reported pain-related discomfort
Haack et al. 2009 [66]	24	7/13	Repeated measurements	Daily reported pain-related discomfort	Questionnaire	5	Total SD	3	Kept awake	Increased reported pain-related discomfort (1st night)
			B–SD–R with control group				Recovery			Decreased reported pain-related discomfort
Tiede et al. 2010 [24]	10	2/8	Repeated measurements B–SD	Heat pain stimulations at same intensity	Laser	2	Partial SD	1	At-home control with actigraphy	Increased reported pain response to heat stimulation
Schey et al. 2007 [70]	10	5/5	Two groups (healthy volunteers and patients with gastroesophageal reflux)	Gastroesophageal pain sensitivity	Esophageal acid perfusion	1	Partial SD	1	At-home control with actigraphy	No change
Azevedo et al. 2011 [13]	28	0/28	Repeated measurements	Heat pain threshold	Laser	2–4	Total SD	2	Keep awake	Increased reported pain response to heat stimulation (after second night)
			B–SD–R	Stimulations at same pain intensity						No change in heat pain threshold
			Three groups (with control group)				REM SD	4	Auditory stimulation and woken	No change
							Recovery	1		Decreased reported pain response to heat stimulation (Total SD)
Irwin et al. 2012 [68]	27	21/6	Comparison with patient group	Daily reported pain-related discomfort	Questionnaire	4	Partial SD	1	Sleep restriction	Increased reported daily pain-related discomfort
							Recovery			Decreased reported daily pain-related discomfort
Schuh-Hofer et al. 2013 [71]	14	6/8	Repeated measurements	Mechanical, heat, and cold pain threshold	Algometer	1	Total SD	1	Kept awake	Decrease in mechanical, heat, and cold pain threshold
			B–SD	Quantitative Sensory Testing	Thermode					
					Quantitative Sensory Testing					No change in reported daily pain-related discomfort

B–SD–R: basal, sleep deprivation and recovery nights; REM SD: rapid eye deprivation; SWSD: slow wave sleep deprivation.

Table 3
Studies on the effects of sleep deprivation on pain in different patient populations.

Authors	Population	*n*	Design	Pain measurement	Methods	Recorded nights	Sleep intervention	Methods	SD nights	Main results
Schey et al. 2007 [70]	Patients with gastroesophageal reflux	10	Control group (patients and healthy volunteers)	Gastroesophageal pain sensitivity	Esophageal acid perfusion	1	Partial SD	Sleep restriction	1	Increased reactivity to pain Increased intensity rating
Kundermann et al. 2008 [72]	Patients with major depressive symptoms	19	Control group (same patients)	Heat and cold pain threshold Daily reported pain-related discomfort	Thermode questionnaire	11	Total SD	Kept awake	Six non-consecutive nights	Decreased reported cold and heat threshold Increased reported daily pain-related discomfort
Irwin et al. 2012 [68]	Patients with rheumatoid arthritis	27	Control group (healthy volunteers)	Daily reported pain-related discomfort	Questionnaire	4	Partial SD recovery	Sleep restriction	1	Increased reported daily pain-related discomfort for partial SD, and higher than healthy subjects Decreased reported daily pain-related discomfort
Busch et al. 2012 [73]	Patients with chronic somatoform pain	20	Repeated measurements SD–R	Heat and cold pain threshold Daily reported pain-related discomfort	Thermode questionnaire	2	Total SD recovery	Kept awake	1	Increased reported daily pain-related discomfort No change in mechanical or thermal pain threshold Increased mechanical and thermal pain threshold

several experimental studies have explored the relationship between sleep and pain. In one research stream, nociceptive stimulations were used to disturb sleep in experimental settings, and in another stream, sleep deprivation, restriction, and disruption were used to explore the impact of altered sleep on the pain process.

Alterations in the pain process in response to sleep disruptions: studies in healthy subjects and in different patient populations

Since the publication of an extensive review in 2006 [16] on the effect of sleep disruptions on the pain process (eight studies), 10 further experimental studies in healthy volunteers have been performed (see Table 2) [10–14,17–20,24,62,65–71]. The relationship between sleep disruptions and the pain process was also tested in different patient populations, including patients with major depression [72], rheumatoid arthritis [68], somatoform pain [73], and gastroesophageal reflux [27] (Table 3). Overall, most of the results indicated that sleep disruption, specific sleep stage deprivations or sleep continuity disturbances altered pain perception and caused pain.

These results demonstrated that total (two of three studies) [62,66,71] and partial (seven of nine studies) [12,14,17–19,62,67–69] sleep deprivation (SD) induced pain-related discomfort such as stiffness, joint pain, back pain, and headache in healthy volunteers, whereas recovery nights were associated with decreased intensity of discomfort [18,19,62,68]. Similar results were also found in patients with major depression [72], rheumatoid arthritis [68], and somatoform pain [73].

Nevertheless, some discrepancies remain in the literature on the effect of SD on pain perception, with some studies finding no significant effects on pain perception after sleep disruptions [12,62,65]. These discrepancies could be explained by different methods used to alter sleep (total SD, sleep restriction, forced awakening, or auditory stimulation), methods to assess pain perception (heat, cold, or mechanical pain stimulation), and study designs (repeated measurements, with or without a control group, and other complex designs), as well as wide interindividual differences (e.g., age, gender). Regarding partial SD, in negative studies [12,65,69], auditory stimulation during SWS was used (during stage 4 only of Rechtschaffen and Kales standardized scoring [74]), which would not suffice for sleep deprivation. Forced awakening (i.e., subjects awakened 20 min every hour of sleep plus one full hour during sleep) was also used, and showed greater capacity to cause pain and induce the dysfunctional pain-inhibition system (measured by DNIC) compared to simple sleep restriction [62].

In order to assess pain perception, different tools (pain threshold vs. pain stimulation) have been used to explore how altered sleep affects the pain process. Sensitivity (pain threshold) has been the most frequently tested indicator, and mechanical threshold (algometer, four of eight studies) [12,17–20,62,69,71] and heat pain threshold (thermode stimulations or bulb exposure, three of six studies) [10,11,13,20,65,71] appear to decrease after SD. More recently, in healthy subjects, two studies used heat laser stimulation to show that stimulation at a same intensity was perceived as more intense after partial or total SD [13,24], one recent study showed that total SD results in a generalized decrease in mechanical, cold, and heat pain threshold [71], suggesting that SD induces hyperalgesia.

It was also proposed that SWS and REM sleep play specific roles in diurnal pain control [11,16]. Specific SWS deprivation caused a decrease in the mechanical pain threshold in three of seven studies [11,12,17–20,69] and induced pain-related discomfort in four of five studies [12,17–19,69]. Only a few studies have addressed REM SD, and only one (of three studies) showed decreased heat pain threshold [11,13,20]. Although only a few studies have focused on REM sleep, these divergent results do not support a specific sleep

stage role in diurnal pain control. Moreover, Onen and collaborators [20] deprived volunteers of both SWS and REM sleep and found no specific effect of either sleep stage deprivation. Moreover, Smith and collaborators [62] found that sleep continuity disruptions impaired the endogenous pain-inhibitory function with an increased pain-related discomfort, an effect not replicated with simple sleep restriction. Thus, it remains unclear as to whether alterations in the pain process are due to specific sleep stage deprivation or to sleep continuity disturbance.

A possible explanation for altered pain control caused by sleep disruptions could be attention, which is an important modulator of the pain experience [75]. Tiede and collaborators [24] showed that sleep disruptions were associated with a significantly weaker ability to disengage oneself from painful stimulation. The inflammatory process was also proposed as a contributor to altered pain processes. Haack and collaborators [67] showed that pro-inflammatory mediators (IL-6) increased in prolonged sleep restriction, associated with pain-related discomfort. Finally, pain is a sensory and emotional experience that triggers a physiological and psychological reaction. Thus, pain is influenced by anxiety and emotional state [76]. Sleep loss not only enhances pain but also alters emotional well-being, which is an integral part of the pain experience [14,77], and sleep disruption in particular [78] is known to promote a negative emotional state such as anxiety, suggesting that it indirectly amplifies pain.

Sleep disruptions in response to experimental pain during sleep: studies in healthy subjects and patients

Nociceptive experimental stimulations were applied in human sleep to challenge pain perception specificity during sleep, producing abrupt central nervous system reactivity (for a recent review on nociception response during sleep, see Mazza et al. [79]). These stimulations produced electroencephalographic activation (27–48% of cases), according to the type of nociceptive stimuli (intramuscular infusions, thermal or laser stimulations) [27,29,30]. In healthy subjects, these nociceptive stimuli have induced cortical arousals in all sleep stages (Fig. 2) [27,29]. However, the temperature intensity required to awaken participants in sleep stage 2 must be increased by 1 °C to produce a similar response during SWS or REM sleep [51]. Central nervous system reactivity to nociceptive stimuli delivered during sleep was accompanied by a concomitant sympathetic reactivity, well known during wakefulness [80–83] and which changes the physiological processes under autonomic control [28,84]. This sympathetic reactivity, which was of higher amplitude than with non-nociceptive stimuli [84], was also preserved in all sleep stages, and was closely related to electroencephalographic activation. However, when nociceptive stimulations did not produce cortical arousals, sympathetic reactivity remained at lower magnitude [28].

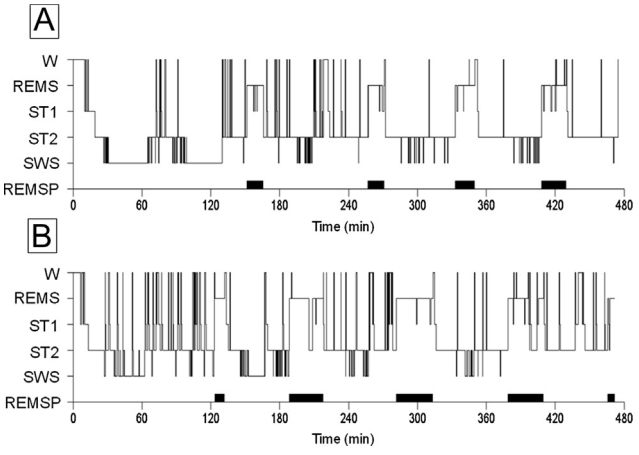

Fig. 2. Consequences of repetitive nociceptive stimulation on sleep continuity (hypnogram) in a healthy subject. The first hypnogram (A) represents one basal night and the second (B) the experimental night. Note that recurrent (50 stimulations per hour) heat nociceptive stimulation during sleep (by thermode, 7 s of stimulation, moderate pain intensity previously estimated during wakefulness) induced frequent arousals in this volunteer and altered sleep continuity without preventing normal sleep patterns or inherent sleep cycle rhythms. W: wakefulness; ST1: sleep stage 1; ST2: sleep stage 2; SWS: slow wave sleep; REMS: rapid eye movement sleep; REMSP: rapid eye movement sleep period.

These studies showed that experimental pain during sleep in healthy volunteers induces sleep fragmentation, characterized by abrupt activation of the central nervous system, producing electroencephalographic activation and concomitant changes in physiologic parameters under autonomic control, such as cardiovascular and respiratory systems.

Alterations in the pain process in response to sleep disruptions: studies in animals

Experimental studies in animals show much more consistent results (for a review, see Lautenbacher and collaborators [16]), and these results suggest that REM sleep deprivation amplifies the pain response in animals and appears to block the analgesic effect [85]. However, the small number of studies on SWS deprivation in animals [16,86,87] does not allow drawing conclusions about the potential effects of SWS disruptions or non-specific sleep disruptions. It is therefore possible that the observed effects are due to sleep continuity disturbances, that is, from light to deep sleep and to REM ultradian cycles. Moreover, the technique used (platform-on-water or “flower pot”) in animal studies could also alter non-REM sleep, and is known to induce stress in animals. [88]

Sleep disruptions and opioid use

Opioids, which are analgesic agents commonly used to treat postoperative pain, are known to affect sleep [31,89,90]. Moreover, they could also have painful side effects in the postoperative period in association with prolonged ileus or bladder retention. Opioids may also disrupt breathing [91], and they constitute a major concern in patients with sleep apnea [92,93]. In addition to the above-described factors reported to increase sleep complaints and sleep disruptions measured by polygraphy, the concomitant use of opioids to manage postoperative pain is a further putative exacerbating factor.

Importantly, we recognize that opioids are powerful agents to reduce postoperative pain, and rather than contraindicating their use, the aim is instead to raise awareness of the potential effects on sleep architecture, continuity, and breathing. Much evidence supports the potentially deleterious influence of opioids on sleep [31,32,90]. With acute administration to healthy, pain-free volunteers, opioids (morphine and methadone) reduced both SWS and REM sleep duration and promoted wakefulness [31]. This influence appears to be dose-dependent: low doses reduced SWS whereas higher doses reduced both SWS and REM sleep. However, opioids, particularly long-acting opioids, also improved sleep [94]. This apparent contradiction suggests that both the time and dosage of opioids could interfere with circadian and sleep processes [95]. Therefore, sleep and wake states could be disturbed by both pain and by clinical pain management with opioids. In patients at risk for sleep disturbance, alternatives should be considered, such as non-steroidal anti-inflammatory medications, which appear to have a less deleterious influence on sleep [60].

The fact that a number of patients in surgery lose both SWS and REM sleep supports the observations of opioid effects on sleep in healthy volunteers. Nevertheless, Cronin and colleagues [36], in a study in 10 women undergoing benign gynecological surgery with or without opioids (fentanyl), showed only a light opioid effect on SWS duration, and none on REM sleep duration. These results should be replicated in further studies with larger samples, using various opioid doses and types, administered at different times, and in different postsurgical populations.

Sleep disruptions and pain in the postoperative period

In a postsurgical study, Knill and colleagues [41] conducted polysomnographic recordings after cholecystectomy to investigate the relationship between pain and sleep. They found higher pain intensity (assessed each evening on a visual analog scale (VAS)) and higher opioid dosage (at night) when sleep was most severely disturbed, with SWS duration decrease, REM sleep abolition, and sleep fragmentation. They also found that REM recovery after surgery corresponded to gradual pain dissipation. In a prospective study, Beydon and collaborators [33] showed that patients who suffered from sleep after orthopedic, vascular, and general surgery explained their unsatisfactory sleep by the presence of noise and pain during the night (reported on a VAS on the last day of hospitalization).

Poor sleep quality the night before surgery has also been shown to cause increased postoperative pain sensitivity. Wright and collaborators [96] found a relationship between sleep efficiency (measured by actigraphy) the night before conservative breast surgery for cancer diagnosis or treatment and self-reported daily pain: patients with lower sleep efficiency the night before surgery also reported higher retrospective pain one week after surgery (Brief Pain Inventory). Despite the small sample size ($n = 24$), this relationship was independent of several confounding factors such as age, race, and use of perioperative analgesics (psychological factors such as preoperative anxiety and depression were not included because they were not related to postoperative pain in the univariate analysis). Mamie and collaborators [7] found that, of several factors known to affect postoperative pain (assessed by VAS, 24 h following the surgery), previous chronic sleep complaints constituted the strongest determinant of pain at rest during the postoperative period, independently of age, gender, surgery type, general anesthesia, high doses of analgesics, expectation, and fear of postoperative pain (depression was not included because it was not related to postoperative pain in the univariate analysis). Concerning postoperative sleep, Kain and Caldwell-Andrews [34], in a study of 92 surgery patients and 35 control subjects, showed that elective surgery patients who suffered from sleep disruptions (decreased sleep efficiency assessed by actigraphy the first and second postoperative nights) also reported higher daily postoperative pain assessed by VAS in the second postoperative day (with no relationship to preoperative anxiety). Büyükyilmaz and collaborators [46] showed a significant relationship between reported pain intensity (by McGill Pain Questionnaire) on the evening of the second postoperative day and sleep quality (Pittsburg sleep quality index) on the third postoperative morning in a correlation study of 75 orthopedic patients under major surgeries. Patients who reported the lowest sleep quality also suffered the highest daily pain intensity. Furthermore, Cremeans-Smith and collaborators [97] showed that postoperative pain and sleep complaints reported at one month after surgery were related to further functional limitations at three months: patients who underwent total knee replacement surgery and who reported higher pain (arthritis impact measurement scale) and sleep (Pittsburg sleep quality index) disruptions at one month after surgery also reported higher functional limitations at three months (Western Ontario and McMaster Universities osteoarthritis index), independently of age, gender, depression, and presurgically reported pain, sleep, and functional limitations.

These studies further support that pre- and postoperative sleep disruptions result in altered pain control and increased likelihood for greater intensity of postoperative pain to a given pain condition.

Conclusion

Clinical, experimental, and epidemiological data support that sleep disruption contribute to exacerbate pain perception and interfere with pain management. Although surgical procedures produce secondary effects such as postoperative pain, and inflammatory responses, sleep disruption probably contributes to the intensity of postoperative pain. Sleep is largely altered in postoperative surgery, especially in certain vulnerable patients, according to genetic and psychological factors. Pain and analgesic agents may in turn contribute to these sleep disturbances in a bidirectional process that could exacerbate the overall perception of pain in the postoperative period. Clinical, experimental, and epidemiological data concur that sleep deprivation contributes to disrupt pain control and exacerbate pain perception. The impact of sleep disturbances on pain control has been underestimated in studies on the predictors of postoperative pain in large cohorts. Further studies are needed to examine the relationship between sleep and spontaneous diurnal pain or opioid consumption on sleep. In particular, the temporal relationship over nights between sleep disruption and the next pain and analgesic dosage needs to be determined in order to validate this hypothesis. A better understanding of the relationship between sleep and pain in the postoperative period would facilitate the development of more effective and safer pain management programs, especially for vulnerable patients who report deep sleep disturbances and who continue to suffer from postoperative pain. By extension, an increasingly common development is a chronic pain condition called persistent postsurgical pain, diagnosed when pain persists after tissue injury and inflammation have healed (about two months after surgery) and when other causes of pain have been excluded [4]. Although several risk determinants have been identified, sleep disturbances have not been considered a risk for some vulnerable patients who develop persistent postsurgical pain. This issue also merits further investigation.

Practice points

- Surgical patients frequently report pain and sleep complaints.
- Sleep patterns can be severely disturbed after surgery: a marked decrease in total sleep time, with decreased duration of slow wave sleep and rapid eye movement sleep stages, and more frequent arousals.
- Both pain and analgesic agents may contribute to altered sleep in the postoperative period.
- Patients reporting a history of chronic sleep problems before surgery are at risk for greater postoperative pain.

Research agenda

- Explore the relationships between sleep and diurnal pain or opioid consumption the following day in post-operative period.
- Examine the role of sleep disturbances in persistent postsurgical pain.
- Assess the benefit of various hypnotic treatments on postoperative pain in patients at risk of severe pain after surgery.

Conflict of interest

None declared.

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